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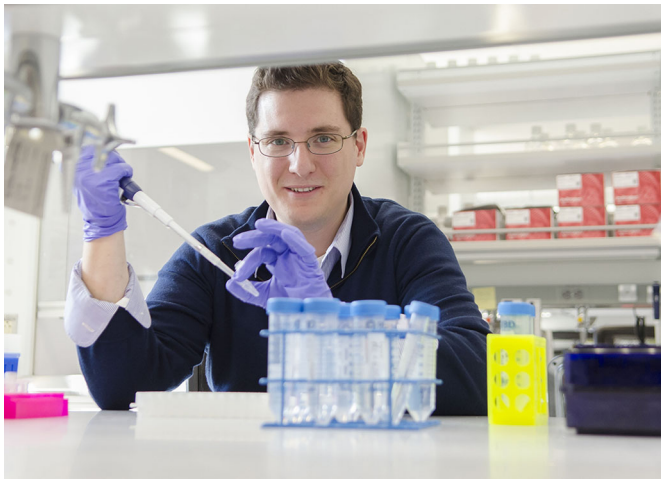
CELL SCIENTISTS TO WATCH

Cell scientist to watch – Mitchell Guttman

Mitchell received a bachelor's degree in molecular and computational biology and a master's degree in computational biology and bioinformatics from the University of Pennsylvania. He then joined the laboratory of Eric Lander at the Broad Institute of MIT and Harvard and was awarded his PhD in 2012. The same year he was named in the Forbes '30 under 30: science and healthcare' list of rising stars and received an NIH early independence award. Mitchell subsequently moved to the California Institute of Technology as an Assistant Professor to establish his own laboratory. He has received numerous awards, including being named a Robertson Investigator of the New York Stem Cell Foundation, an Investigator at the Heritage Medical Research Institute and a Pew-Stewart scholar for cancer research in 2015. Having identified and characterised a new class of functional large non-coding RNA (lncRNA) genes, his laboratory aims to understand the mechanisms by which lncRNAs act to control cellular functions through regulation of proteins, binding to genomic DNA targets and contributing to nuclear organisation.



Portrait of Mitchell Guttman.

What inspired you to become a scientist?

I always enjoyed science and when I was a sophomore [age 15 or 16] in high school, my chemistry teacher encouraged me to take it a step further and explore scientific research. He set me up with people at the Mount Sinai School of Medicine to do research during the summer break. I had the opportunity to work with a clinical pathologist and a basic cancer researcher – a collaboration studying the role of metastasis. Of course what I was able to do as a high school student was very limited, but it was an exhilarating experience because it really gave me the opportunity to see how science was done and I got hooked. My interests morphed quite a bit, but I think that was the starting point for how I got interested in what I'm doing.

You don't have a family background in science?

No, I don't. My siblings and my father are in business, and although my mom's a computer scientist, she's also on the business side of things.

With a degree in both molecular and computational biology, were MIT and the Broad Institute a great match at the time for your interests?

Yes, at the end of my degree I had been working on developing new computational methods to look at cancer genomics. In short, this was something the Broad Institute was very interested in at the time, and particularly Eric Lander. When I joined his lab, he encouraged me to look broader and think more 'basic' – not to focus on the translational end but on something that would solve a more fundamental question in biology. He sent me on a track to start to explore what I wanted to do. And by looking at new aspects of the genome – the unannotated genome – that's when I started to get really interested in long non-coding RNA (lncRNA) questions.

What questions are your lab trying to answer just now?

The simple answer to this question is what makes lncRNAs unique in their ability to control cellular functions. Why does the cell use a lncRNA to carry out certain processes, rather than a protein? Given that there are many thousands of lncRNAs, to grasp what makes them different from proteins from a mechanistic perspective is really central to our understanding of where they might work and why they might be essential for biological processes. An important example of that is the lncRNA *Xist*, which is essential for dosage compensation. When we started working on this, the mechanism of how *Xist* works wasn't clear at all, despite the fact that it had been discovered 25 years ago. We knew a lot about the biological function of X-chromosome inactivation, but not much about how the RNA itself really mediates this process of chromosome-wide silencing. We started to work on the mechanism of this lncRNA, and one of our really important results was the essential role of *Xist* in exploiting and shaping higher-order structures of chromosomes. This led us to focus on the relationship between lncRNAs and 3D genome structure, because how *Xist* localises to DNA and shapes the structure of the chromosome is a key feature that separates the roles that lncRNAs play from the ones that proteins do.

What challenges did you face when starting your own lab that you didn't expect?

I do consider myself particularly lucky because I had a really phenomenally supportive mentor with Eric Lander; I got a lot of great hands-on training from him about how to be an independent scientist and how to think about problems. But nothing quite prepares you for starting your own lab and being solely on your own. I would say the biggest challenge, and the thing that really caught me off guard, was how intellectually lonely it is to start a lab. You're used to being able to bounce around ideas with your fellow lab members and the group leader and discuss things that come up.

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Mitchell with his newborn son, Alex.

Then, you're put into this new environment, given a bunch of money and space and it's just you. All of a sudden, the basic things become harder and that's not even to mention starting from scratch and having to teach everyone who comes into the lab, which all happens at the same time. So it can feel – even in the best scenarios I think – a bit intellectually lonely, but then you get to build the environment that you want, which is the upside.

How are the challenges that you're facing now different?

Now that we have a great group of people who create this stimulating environment again, the challenges are more around the issue of 'you only have so many hours in a day'. Every postdoc or student has an important problem that they're working on, and it becomes harder and harder to become deeply involved in the day-to-day aspects of every project. I would really love to tackle every problem and be engaged in a hands-on way all the time, but that becomes much harder now than it used to be.

"…the biggest challenge, and the thing that really caught me off guard, was how intellectually lonely it is to start a lab."

Speaking of time management, how do you achieve a work–life balance when you're trying to establish yourself as an independent investigator?

You know, you asked that question about when I was starting the lab, and at that time my work–life balance wasn't as existent as it should have been. My wife also had a very busy schedule because she was starting out on a resident position in the US, which is just very time consuming. But now I think we're much better about this – we just had our first child. So our work–life balance is much improved, which is great, but I think an important piece to that is that I also have people in my lab who I fully trust and completely respect. I'm very lucky that I have a really amazing group of people that I work with – things run smoothly regardless of how many hours you can put in in any given day.

What is the best science-related advice you ever received?

There are two bits of advice that I really liked: one relates to thinking about scientific problems, the other one to the group leader transition. When I was trying to find a good problem to work on before I landed on lncRNAs, Eric told me this paraphrase of the famous Wayne Gretsky quote: go after problems that everyone will be interested in, rather than problems that everyone is currently interested in. It's a bit cliché but very, very true. The best transition advice, though, was not to worry about how to compete with senior folks who are Howard Hughes investigators and members of the national academy when you're starting your lab. Rather than thinking about it as a competition, don't get intimidated by the fact that you think someone else might be working on the same problem, because even if they are, ultimately, everyone takes different paths and ends up at very different places. It turned out to be very true and great advice.

What's the most important advice you would give to someone about to start their own lab?

The most important thing you can do when you're starting a new lab is recruit the right people. The people you have in your lab are really what make the scientific, but also the cultural, environment, and the two go hand-in-hand. When you're a small lab and you're starting out, one person who doesn't fit the culture you want to build can really have a huge impact on that culture and change a lot of things scientifically and between colleagues. One of the things that I found to be useful early on was to ask my senior colleagues to meet with candidates and give me their thoughts. This was very helpful because they were often able to spot some really big red flags that I couldn't.

"…don't get intimidated by the fact that you think someone else might be working on the same problem…"

What is your advice on establishing good collaborations?

I 'grew up' at the Broad Institute, which is built around collaborations. For me, collaborative science is what makes science fun; being able to leverage different talents of people and expertise that are complementary to your own to do something even better than you could do on your own. I think the challenge with establishing good collaborations is to only collaborate with people where I feel that we can really synergise, where each of us feels we can benefit 100%. We see collaborations as a non-zero sum, where everyone can benefit from each other without impacting each other and that might sound like a cliché, but it's really not. For example, one of my closest collaborators here in Los Angeles is Kathrin Plath over at UCLA. We share data openly, we even discuss ideas that are not mature and it's a very open communication pipeline, because I would like to think she's benefitted from interacting with us, and I know that we've benefitted tremendously from interacting with her.

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How do you get the most out of the meetings you attend?

I can't say that I had a particularly well-formulated philosophy around meetings when I was starting. I would usually just go to meetings that I thought were of interest to me, and often that was on the periphery of what I was working on. I thought the most valuable thing about going to these meetings was that I could learn about new science and areas that relate to what I care about and try to appreciate things that may not have been obvious to me from just reading papers. I feel there are many projects that we work on now that came out of the fact that I went to post-transcriptional gene regulation or chromatin meetings and learned things from people about the subtle, but important, points not usually discussed in papers. Meet people in your field, but also beyond your field, have conversations with them and that often gives you the opportunity to think more broadly.

Could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?

That's a good question. I'm not a world-class musician or anything. I will say one of the great things about living in Los Angeles is that we have obviously spectacular weather all year round. We have great mountains, bike trails and hiking trails and whatnot. On the weekends I love to take my bike and go to different areas of L.A. – the mountains, the beach, to go and bike in the quiet areas and just reflect. It's not a defining hobby, but it is fun and a big reason my wife and I really wanted to come out to Los Angeles and to California in general.

Mitchell Guttman was interviewed by Manuel Breuer, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.